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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,679	05/17/2007	Jo Klaveness	PN0397	7412

7590 01/25/2012

GE Healthcare,Inc.
101 Carnegie Center
Princeton, NJ 08540

EXAMINER	
SCHLIENTZ, LEAH H	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
01/25/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,679	KLAVENESS ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,8 and 11* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,8 and 11* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/18/2010 has been entered.

Status of Claims

Claim 1 has been amended. Claims 1, 8 and 11 are pending and are examined herein on the merits for patentability.

Response to Arguments

Any rejection not reiterated herein has been withdrawn as being overcome by amendment. New grounds of rejection are set forth herein, necessitated by claim amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeJesus *et al.* (*J. Label Compd. Radiopharm.*, 2003, 46, S1-S403, p. S1) in view of in view of Poss (US 2005/0214221), in further view of Cannizzaro (US 2005/0261253).

DeJesus teaches that more than two thirds of human cancers derive from epithelial tissues and the EFGR-TK is overexpressed in the majority of these tumors. Numerous selective EGFR-TK inhibitors with nanomolar affinities have been developed as potential anti-cancer agents. One potent inhibitor that has progressed the furthest toward clinical registration is ZD1839 (or Iressa). ZD1839 is approved for clinical use in Japan and is close to obtaining U.S. FDA approval. ZD1839 is a fluorine-containing anilinoquinazoline which can be isotopically labelled with ^{18}F for use in clinical oncology as a PET imaging agent. Since extensive pre-clinical and clinical data on ZD1839 are available, the use of ^{18}F-ZD1839 to identify patients who would benefit from Iressa treatment and monitor its efficacy would be straightforward. We recently began the

development of a reliable and efficient synthetic route for the routine preparation of ^{18}F-ZD1839. Initial biodistribution studies in normal HSD-ICR mice showed high uptake of ^{18}F-ZD1839 in the GI tract, liver, kidneys and bladder consistent with the known high EGFR localization in these organs. Plasma metabolite analysis in several mice up to 3 hr showed temporally decreasing percentage of unchanged ^{18}F-ZD1839 declining to 52% at 3 hr postinjection. Dynamic PET studies of mice using a Concorde microPET P4 scanner are underway (abstract).

Accordingly, DeJesus teaches ^{18}F radiolabeling of Iressa for PET imaging, but does not specifically teach providing a reporter detectable in optical imaging for optical imaging of oesophageal cancer.

Poss teaches that nuclear imaging using various radiolabeled molecules has demonstrated some clinical utility in being able to image certain forms of molecular activity. Various radiolabeled metabolite imaging probes to image metabolic activity are known in the art and techniques of using these radiolabeled metabolite imaging probes to image metabolic activity are well established. Specifically, this technique has been used to successfully label and image several different metabolites including deoxyglucose. PET imaging using [^{18}F]fluorodeoxyglucose is well-established clinical cancer imaging method that can be used to detect very small tumors and monitor a patient's response to therapy (paragraph 0004). Although nuclear imaging of radioactively labeled metabolites has demonstrated some clinical utility, there remain significant limitations with these imaging approaches. Specifically, the short half-life of many radionuclides, including ^{18}F, ^{11}C, etc. severely limits the time available for

synthesis and subsequent imaging, and therefore any facilities using these technologies require skilled radiochemists on staff to synthesize the imaging agents immediately prior to use. In the case of PET imaging, a cyclotron is usually required on-site because of the extremely short half-life of most positron-emitting radionuclides, including ^{18}F. In addition, clinical hardware systems required to detect positron and gamma emitting radionuclides are relatively expensive and therefore require a significant upfront capital investment. Because of these limitations, few clinical centers have the necessary expertise, resources, and money to operate a nuclear imaging center effectively (paragraph 0005). Another significant disadvantage to nuclear imaging is that patients are exposed to radioactivity (paragraph 0006). Molecular optical imaging is a new imaging modality that generates molecular images using penetrating light rays. Preferably, light in the red and near infrared range (600-1200 nm) is used to maximize tissue penetration and minimize absorption from natural biological absorbers (paragraph 0007). There is a need for in vivo optical metabolite probes that are safer, less expensive and more convenient than current nuclear imaging probes (paragraph 0011). Optical imaging probes are disclosed having the formula $M(_n)$-F, where M is a metabolically recognizable molecule and F is a fluorochrome. Fluorochromes includes NIRFs having absorption and emission maximum between 600 and 1200 nm (paragraph 0021). Metabolically recognizable small drugs can be used, including drugs that are recognizable by tyrosine kinase (paragraph 0025). In vivo methods for optical imaging are also disclosed, including (a) administering to a subject an optical imaging probe (b) allowing time for the optical imaging probe to reach the target tissue and,

preferably, but not necessary, for molecules in the target tissue to metabolize the probe; (c) illuminating the target tissue with light of a wavelength absorbable by the optical imaging probe; and (d) detecting the optical signal emitted by the optical imaging probe (paragraph 0032). The methods can be used in the detection, characterization and/or determination of the localization of a disease, especially early disease, including all types of cancer (paragraph 0038). Exemplary fluorochromes include Cy5.5, Cy5, Cy7, AlexaFluor, indocyanine green, etc (paragraph 0072).

Cannizzaro teaches phosphorous substituted kinase inhibitory compounds (abstract). It is known that class 1 kinases such as the EGF family of receptor tyrosine kinases are frequently present in common human cancers, such as breast cancer, oesophageal cancer, etc., and that is known that EGF type tyrosine kinase activity is rarely detected in normal cells, whereas it is more frequently detected in malignant cells (paragraph 0008, see also 0027). Intracellular targeting may be achieved that allow accumulation or retention of biologically active agents inside cells. The invention provides analogues of kinase-inhibitory compounds, such as disclosed in paragraphs 0030-0115. The compounds can be bound to a label, including fluorophores (paragraph 0578).

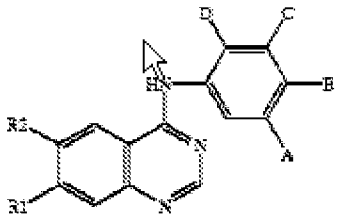
It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute a NIRF label for ^{18}F on ZD1830 (Iressa) inhibitors disclosed by DeJesus, and to perform optical imaging therewith when the teaching of DeJesus is taken in view of Poss. One would have been motivated to do so because Poss teaches that targeted optical imaging probes are superior to radiolabeled probes because of

increased convenience (no need for on-site radiosynthesis), decreased cost, and increased safety (patients are not exposed to radioactivity). One would have had a reasonable expectation of success in doing so because both DeJesus and Poss are directed to molecular imaging methods, and because Poss teaches that a variety of targeting moieties can be conjugated to fluorochromes, including drugs that are recognizable by tyrosine kinase. While DeJesus teaches that a variety of human cancers derive from epithelial tissues and the EGFR-TK is overexpressed in the majority of these tumors, it is not specifically recited that imaging of oesophageal cancer is performed. However, it is known in the art that the EGF family of receptor tyrosine kinases are frequently present in oesophageal cancer, but that EGF tyrosine kinase activity is rarely detected in normal cells, as shown by Cannizaro. Accordingly, one of ordinary skill performing optical imaging using EGFR-TK inhibitor probes would have a reasonable expectation that such probes would distribute to oesophageal cancer. Optical imaging using targeted fluorochrome probes can be used in the detection, characterization and/or determination of the localization of a disease, including cancer, as shown by Poss.

Claims 1, 8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mishani (US 6,126,917) in view of Poss (US 2005/0214221), in further view of Cannizzaro (US 2005/0261253).

Mishani teaches fluorinated positron emission tomography biomarkers (PET) for quantification of epidermal growth factor receptor kinase. PET, a nuclear medicine

technology which allows three-dimensional, quantitative determination of the distribution of radioactivity within the human body. A radiotracer that binds to EGFR-TK might allow mapping and quantification of this receptor-kinase, which would allow study of changes in expression levels of this receptor, including monitoring the response to hormonal or chemotherapy (column 1, lines 1-35). Compounds of the formula below are disclosed, including ^{18}F at position A or B, for example (column 3, lines 25+).



Methods of monitoring the level of epidermal growth factor receptor within a body of a patient comprising a) administering to the patient a radiolabeled compound above, and b) employing nuclear imaging technique for monitoring distribution of the compound within the body. Pharmaceutical carriers are disclosed (column 4, lines 1-18).

Mishani teaches PET imaging, rather than optical imaging with labeled EGFR-TK inhibitors.

Poss teaches that nuclear imaging using various radiolabeled molecules has demonstrated some clinical utility in being able to image certain forms of molecular activity. Various radiolabeled metabolite imaging probes to image metabolic activity are known in the art and techniques of using these radiolabeled metabolite imaging probes to image metabolic activity are well established. Specifically, this technique has been used to successfully label and image several different metabolites including

deoxyglucose. PET imaging using [^{18}F]fluorodeoxyglucose is well-established clinical cancer imaging method that can be used to detect very small tumors and monitor a patient's response to therapy (paragraph 0004). Although nuclear imaging of radioactively labeled metabolites has demonstrated some clinical utility, there remain significant limitations with these imaging approaches. Specifically, the short half-life of many radionuclides, including ^{18}F, ^{11}C, etc. severely limits the time available for synthesis and subsequent imaging, and therefore any facilities using these technologies require skilled radiochemists on staff to synthesize the imaging agents immediately prior to use. In the case of PET imaging, a cyclotron is usually required on-site because of the extremely short half-life of most positron-emitting radionuclides, including ^{18}F. In addition, clinical hardware systems required to detect positron and gamma emitting radionuclides are relatively expensive and therefore require a significant upfront capital investment. Because of these limitations, few clinical centers have the necessary expertise, resources, and money to operate a nuclear imaging center effectively (paragraph 0005). Another significant disadvantage to nuclear imaging is that patients are exposed to radioactivity (paragraph 0006). Molecular optical imaging is a new imaging modality that generates molecular images using penetrating light rays. Preferably, light in the red and near infrared range (600-1200 nm) is used to maximize tissue penetration and minimize absorption from natural biological absorbers (paragraph 0007). There is a need for in vivo optical metabolite probes that are safer, less expensive and more convenient than current nuclear imaging probes (paragraph 0011). Optical imaging probes are disclosed having the formula $M_{(n)}$-F, where M is a

metabolically recognizable molecule and F is a fluorochrome. Fluorochromes includes NIRFs having absorption and emission maximum between 600 and 1200 nm (paragraph 0021). Metabolically recognizable small drugs can be used, including drugs that are recognizable by tyrosine kinase (paragraph 0025). In vivo methods for optical imaging are also disclosed, including (a) administering to a subject an optical imaging probe (b) allowing time for the optical imaging probe to reach the target tissue and, preferably, but not necessary, for molecules in the target tissue to metabolize the probe; (c) illuminating the target tissue with light of a wavelength absorbable by the optical imaging probe; and (d) detecting the optical signal emitted by the optical imaging probe (paragraph 0032). The methods can be used in the detection, characterization and/or determination of the localization of a disease, especially early disease, including all types of cancer (paragraph 0038). Exemplary fluorochromes include Cy5.5, Cy5, Cy7, AlexaFluor, indocyanine green, etc (paragraph 0072).

Cannizzaro teaches phosphorous substituted kinase inhibitory compounds (abstract). It is known that class 1 kinases such as the EGF family of receptor tyrosine kinases are frequently present in common human cancers, such as breast cancer, oesophageal cancer, etc., and that is known that EGF type tyrosine kinase activity is rarely detected in normal cells, whereas it is more frequently detected in malignant cells (paragraph 0008, see also 0027). Intracellular targeting may be achieved that allow accumulation or retention of biologically active agents inside cells. The invention provides analogues of kinase-inhibitory compounds, such as disclosed in paragraphs

0030-0115. The compounds can be bound to a label, including fluorophores (paragraph 0578).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute a NIRF label on radiolabeled EGFR-TK inhibitors disclosed by Mishani, and to perform optical imaging therewith when the teaching of Mishani is taken in view of Poss. One would have been motivated to do so because Poss teaches that targeted optical imaging probes are superior to radiolabeled probes because of increased convenience (no need for on-site radiosynthesis), decreased cost, and increased safety (patients are not exposed to radioactivity). One would have had a reasonable expectation of success in doing so because both Mishani and Poss are directed to molecular imaging methods, and because Poss teaches that a variety of targeting moieties can be conjugated to fluorochromes, including drugs that are recognizable by tyrosine kinase. While Mishani teaches monitoring the level and distribution of epidermal growth factor receptor within a body of a patient with EGFR-TK inhibitors, it is not specifically recited that imaging of lung cancer is performed. However, it is known in the art that the EGF family of receptor tyrosine kinases are frequently present in oesophageal cancer, but that EGF tyrosine kinase activity is rarely detected in normal cells, as shown by Cannizaro. Accordingly, one of ordinary skill performing optical imaging using EGFR-TK inhibitor probes would have a reasonable expectation that such probes would distribute to oesophageal cancer. Optical imaging using targeted fluorochrome probes can be used in the detection, characterization

and/or determination of the localization of a disease, including cancer, as shown by Poss.

Double Patenting

Claims 1, 8 and 11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7, 8 and 11 of copending Application No. 10/582,893 in view of US 2006/0067947. Both sets of claims are drawn to methods of optical imaging comprising administering an optical imaging contrast agent having overlapping chemical structures V-L-R. While the instant claims recite imaging of oesophageal cancer and the claims of the '679 application recite imaging of lung cancer, it would have been obvious to one of ordinary skill in the art at the time of the invention to provide V-L-R for imaging lung cancer or esophageal cancer when the claims are taken in view of US 2006/0067947 which shows that Iressa (corresponding to variable R in both applications) may treat either lung cancer or esophageal cancer, among others (paragraph 0099). Accordingly, the claims are overlapping in scope and are obvious variants of one another. This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-

9928. The examiner can normally be reached on Monday-Wednesday 9 AM-5 PM and telework Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LHS/

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618